Amendments to the Specification:

Please insert the Sequence Listing being filed concurrently herewith into the specification.

Please amend the paragraph on page 19, lines 4-10 as shown below:

An oligonucleotide of the sequence:

Oligomer 1: TTG CTT* CCA TCT TCC TCG TC (SEQ ID NO: 1)

wherein T* represents a nucleotide functionalized to included a cholic acid linked via a linker to the heterocyclic base of a 2'-deoxyuridine nucleotide was prepared in a 1 μmol scale. Oligomer 1 is useful as an HPV antisense oligonucleotide.

Please amend the paragraph on page 19, line 32 through page 20, line 3 as shown below:

A phosphorothioate oligonucleotide having cholic acid attached to its 5'-terminus of the oligonucleotide sequence:

Oligomer 2:

5'-CHA-CsTsGs $T_sC_sT_s$ $C_sC_sA_s$ $T_sC_sT_s$ $T_sC_sA_s$ C_sT (SEQ ID NO: 2)

wherein CHA represents cholic acid and the subscript "s" represents a phosphorothioate internucleotide backbone linkage was prepared.

Please amend the paragraph on page 21, lines 5-11 as shown below:

A phosphorothioate oligonucleotide having cholic acid attached to its 3'- terminus of the oligonucleotide sequence:

Oligomer 3:

$C_sT_sG_s$ $T_sC_sT_s$ $C_sC_sA_s$ $T_sC_sC_s$ $T_sC_sT_s$ $T_sC_sA_s$ C_sT 3'-CHA (SEQ ID NO: 3)

wherein CHA represents cholic acid and the subscript "s" represents a phosphorothioate internucleotide backbone linkage was prepared.

Please amend the paragraph on page 21, line 33 through page 22, line 5 as shown below:

A phosphorothioate oligonucleotide having cholic acid attached to its 3'- terminus of the oligonucleotide sequence:

Oligomer 4:

$T_sG_sG_s$ $G_sA_sG_s$ $C_sC_sA_s$ $T_sA_sG_s$ $C_sG_sA_s$ G_sG_sC 3'-CHA (SEQ ID NO: 4)

wherein CHA represents cholic acid and the subscript "s" represents a phosphorothioate internucleotide backbone linkage was prepared in the same manner as for the oligonucleotide of Example 4-A-2.

Please amend the paragraph on page 22, lines 9-18 as shown below:

A phosphorothioate oligonucleotide having cholic acid attached to both of the 3'-terminus and the 5'- terminus of the oligonucleotide sequence:

Oligomer 5:

5'-CHA $C_sT_sG_s$ $T_sC_sT_s$ $C_sC_sA_s$ $T_sC_sT_s$ $T_sC_sA_s$ C_sT 3'-CHA (SEQ ID NO: 5)

wherein CHA represents cholic acid and the subscript "s" represents a phosphorothioate internucleotide backbone linkage was synthesized on a 3 x 1.0 μmol scale. Oligomer 5 has the same sequence as Oligomer 1 except for the cholic acid functionalization.

Please amend the paragraph on page 23, lines 19-28 as shown below:

Phosphorothioate oligonucleotides having cholic acid attached to either the 3'-terminus end or the 5'-terminus end of the oligonucleotide sequence and further being uniformly functionalized to include a 2'-O-methyl group on each of the nucleotides of the oligonucleotide were synthesized. The following oligonucleotides having uniform 2'-O-methyl substitutions were synthesized:

Oligomer 6: 5'-CHA CCC AGG CUC AGA 3' (SEQ ID NO: 6) ;

Oligomer 7: 5' CCC AGG CUC AGA 3'-CHA (SEQ ID NO: 7) ; and

Oligomer 8: 5'-CHA GAG CUC CCA GGC 3' (SEQ ID NO: 8).

Please amend the paragraph on page 25, line 19 through page 26, line 3 as shown below:

The following oligonucleotides having phosphodiester inter-nucleotide linkages were synthesized:

Oligomer 9: 5' TA*G 3';

Oligomer 10: 5' CCA* G 3';

Oligomer 11: 5' GGC TGA* CTG CG 3' (SEQ ID NO: 9) ;

Oligomer 12: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 10) ; and

Oligomer 13: CTG TCT CCA* TCC TCT TCA* CT (SEQ ID NO: 11)

wherein A* represents a nucleotide functionalized to incorporate a pentyl-N-phthalimido functionality. Oligomers 12 and 13 are antisense compounds to the E2 region of the bovine papilloma virus-1 (BPV-1). Oligomers 12 and 13 have the same sequence as Oligomer 3 except for the 2' modification. The oligonucleotides were synthesized in either a 10 μmol scale or a 3 x 1 μmol scale in the "Trityl-On" mode. Standard deprotection conditions (30% NH_4OH, 55°C, 24 hr) were employed. The oligonucleotides were purified by reverse phase HPLC (Waters Delta-Pak C_4 15 μm, 300A, 25x100 mm column equipped with a guard column of the same material). They were detritylated and further purified by size exclusion using a Sephadex G-25 column. NMR analyses by both proton and phosphorus NMR confirmed the expected structure for the Oligomers 9 and 10.

Please amend the paragraph on page 26, lines 6-32 as shown below:

The following oligonucleotides having phosphorothioate inter-nucleotide linkages were synthesized:

Oligomer 14:

$T_sT_sG_s$ $C_sT_sT_s$ $C_sC_sA^*_s$ $T_sC_sT_s$ $T_sC_sC_s$ $T_sC_sG_s$ T_sC (SEQ ID NO: 12);

Oligomer 15:

$T_sG_sG_s$ $G_sA_sG_s$ $C_sC_sA_s$ $T_sA_sG_s$ $C_sG_sA^*_s$ G_sG_sC (SEQ ID NO: 13); and

Oligomer 16:

$T_sG_sG_s$ $G_sA^*_sG_s$ $C_sC_sA^*_s$ $T_sA^*_sG_s$ $C_sG_sA^*_s$ G_sG_sC (SEQ ID NO: 14)

wherein A* represents a nucleotide functionalized to incorporate a pentyl-N-phthalimido functionality and the subscript "s" represents a phosphorothioate inter-nucleotide backbone linkage. Oligomer 14 is an antisense compound directed to the E2 region of the

bovine papilloma virus-1 (BPV-1). Oligomers 15 and 16 are antisense compounds to ICAM. Oligomer 14 has the same sequence as Oligomer 3 except for the 2' modification whereas Oligomers 15 and 16 have the same sequence as Oligomer 4 except for the 2' modification. These oligonucleotides were synthesized as per the method of Example 7-B except during the synthesis, for oxidation of the phosphite moieties, the Beaucage reagent (see Example 3 above) was used as a 0.24 M solution in anhydrous CH_3CN solvent. The oligonucleotides were synthesized in the "Trityl-On" mode and purified by reverse phase HPLC utilizing the purification procedure of Example 7-B.

Please amend the paragraph on page 26, line 35 through page 27, line 19 as shown below:

The following oligonucleotides having 2'-O-methyl groups on each nucleotide not functionalized with a 2'-protected amine functionalization were synthesized:

Oligomer 17: CCA A*GC CUC AGA (SEQ ID NO: 15); and

Oligomer 18: CCA GGC UCA GA*T (SEQ ID NO: 16)

wherein A* represents a nucleotide functionalized to incorporate a pentyl-N-phthal-imido functionality and where the remaining nucleotides except the 3'-terminus nucleotide are each 2'-O-methyl derivatized nucleotides. The 3'-terminus nucleotide in both Oligomers 17 and 18 is a 2'-deoxy nucleotide. Both Oligomers 17 and 18 are antisense compounds to the HIV-1 TAR region. The oligonucleotides were synthesized as per the method of Example 6 utilizing Compound 2 for introduction of the nucleotides containing the pentyl-N-phthalimido functionality and appropriate 2-O-methyl phosphoramidite nucleotides from Chemgenes Inc. (Needham, MA) for the remaining RNA nucleotides. The 3'-terminus terminal 2'-deoxy nucleotides were standard phosphoamidites utilized for the DNA synthesizer. The oligonucleotides were deprotected and purified as per the method of Example 7-B.

Please amend the paragraph on page 27, line 24 through page 28, line 11 as shown below:

About 10 O.D. units (A_{260}) of Oligomer 12 (see Example 7) (approximately 60 nmols based on the calculated extinction coefficient of 1.6756×10^5) was dried in a microfuge tube. The oligonucleotide was dissolved in 200 µl of 0.2 M $NaHCO_3$ buffer and D-biotin-N-hydroxysuccinimide ester (2.5 mg, 7.3 µmols) (Sigma, St. Louis, MO) was added followed by 40 µl DMF. The solution was let stand overnight. The solution was applied to a Sephadex G-25 column (0.7 x 15 cm) and the oligonucleotide fractions were combined. Analytical HPLC showed nearly 85% conversion to the product. The product was purified by HPLC (Waters 600E with 991 detector, Hamilton PRP-1 column 0.7 x 15 cm; solvent A: 50 mM TEAA pH 7.0; B: 45 mM TEAA with 80% acetonitrile: 1.5 ml flow rate: Gradient: 5% B for first 5 mins., linear (1%) increase in B every minute thereafter) and further desalted on Sephadex G-25 to give the oligonucleotide:

Oligomer 19: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 17)

wherein A* represents a nucleotide functionalized to incorporate a biotin functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

2. Multiple Site Modification

Please amend the paragraph on page 28, lines 12-26 as shown below:

About 10 O.D. units (A_{260}) of Oligomer 13 (see Example 7, approximately 60 nmols) was treated utilizing the method of Example 8-A-1 with D-biotin-N-hydroxysuccinimide ester (5 mg) in 300 µl of 0.2 M $NaHCO_3$ buffer/ 50 µl DMF. Analytical HPLC showed 65% of double labeled oligonucleotide product and 30% of single labeled products (from the two available reactive sites). HPLC and Sephadex G-25 purification gave the oligonucleotide:

Oligomer 20: CTG TCT CCA* TCC TCT TCA* CT (SEQ ID NO: 18)

wherein A* represents nucleotides functionalized to incorporate a biotin functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times for this product (and its accompanying singly labeled products) are shown in Table 1 below.

Please amend the paragraph on page 28, line 29 through page 29, line 16 as shown below:

A 1M Na_2CO_3/1M $NaHCO_3$ buffer (pH 9.0) was prepared by adding 1M $NaHCO_3$ to 1 M Na_2CO_3. 200 µl of this buffer was added to 10 O.D. units of Oligomer 12 (see Example 7) in a microfuge tube. 10 mg of fluorescein-isocyanate in 500 µl DMF was added to give a 0.05 M solution. 100 µl of the fluorescein solution was added to the oligonucleotide solution in the microfuge tube. The tube was covered with aluminum foil and let stand overnight. The reaction mixture was applied to a Sephadex G-25 column (0.7 x 20 cm) that had been equilibrated with 25% (v/v) ethyl alcohol in water. The column was eluted with the same solvent. Product migration could be seen as a yellow band well separated from dark yellow band of the excess fluorescein reagent. The fractions showing absorption at 260 nm and 485 nm were combined and purified by HPLC as per the purification procedure of Example 8-A-1. Analytical HPLC indicated 81% of the desired doubly functionalized oligonucleotide. The product was lyophilized and desalted on Sephadex to give the oligonucleotide:

Oligomer 21: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 19)

wherein A* represents a nucleotide functionalized to incorporate a fluorescein functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

Please amend the paragraph on page 29, lines 18-31 as shown below:

10 O.D. units (A_{260}) of Oligomer 13 (from Example 7) was dissolved in 300 µl of the 1M Na_2HCO_3/ 1M Na_2CO_2 buffer of Example 8-B-1 and 200 µl of the fluorescein-isothiocyanate stock solution of Example 8-B-1 was added. The resulting solution was treated as per Example 8-B-1. Analytical HPLC indicated 61% of doubly labeled product and 38% of singly labeled products. Work up of the reaction gave the oligonucleotide:

Oligomer 22: CTG TCT CCA* TCC TCT TCA* CT (SEQ ID NO: 20)

wherein A* represents nucleotides functionalized to incorporate a fluorescein functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

Please amend the paragraph on page 29, line 35 through page 30, line 10 as shown below:

10 O.D. units (A_{260}) of Oligomer 12 (see Example 7) was treated with cholic acid-NHS ester (Compound 1, 5 mg, 9.9 μmols) in 200 μl of 0.2 M $NaHCO_3$ buffer/ 40 μl DMF. The reaction mixture was heated for 16 hrs at 45°C. The product was isolated as per the method of Example 8-A-1. Analytical HPLC indicated > 85% product formation. Work up of the reaction gave the oligonucleotide:

Oligomer 23: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 21)

wherein A* represents a nucleotide functionalized to incorporate a cholic acid functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

Please amend the paragraph on page 30, lines 12-26 as shown below:

10 O.D. units (A_{260}) of Oligomer 13 (see Example 7) was treated with cholic acid-NHS ester (Compound 1, 10 mg, 19.8 μmols) in 300 μl of 0.2 M $NaHCO_3$ buffer/ 50 μl DMF. The reaction mixture was heated for 16 hrs at 45°C. The product was isolated as per the method of Example 8-A-1. Analytical HPLC revealed 58% doubly labeled product, 17% of a first singly labeled product and 24% of a second singly labeled product. Work up as per Example 8-A-1 gave the oligonucleotide:

Oligomer 24: CTG TCT CCA* TCC TCT TCA* CT (SEQ ID NO: 22)

wherein A* represents nucleotides functionalized to incorporate a cholic acid functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

Please amend the paragraph on page 30, line 29 through page 31, line 5 as shown below:

10 O.D. units (A_{260}) of Oligomer 12 (see Example 7) was treated with digoxigenin-3-O-methylcarbonyl-ε-aminocaproic N-hydroxy succinimide ester (Boehringer Mannheim Corporation, Indianapolis, IN) in 200 μl of 0.1 M borate pH 8.3 buffer/ 40 μl DMF. The reaction mixture was let stand overnight. The product was isolated as per the method of Example 8-A-1. Work up of the reaction gave the oligonucleotide:

Oligomer 25: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 23)

wherein A* represents a nucleotide functionalized to incorporate a digoxigenin functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

Please amend the paragraph on page 31, lines 7-20 as shown below:

10 O.D. units (A_{260}) of Oligomer 13 (see Example 7) was treated with digoxigenin-3-O-methylcarbonyl-ε-aminocaproic N-hydroxy succinimide ester (Boehringer Mannheim Corporation, Indianapolis, IN) in 300 µl of 0.1 M borate pH 8.3 buffer / 50 µl DMF. The reaction mixture was let stand overnight. The product was isolated as per the method of Example 8-A-1. Work up as per Example 8-A-1 gave the oligonucleotide:

Oligomer 26: CTG TCT CCA* TCC TCT TCA* CT (SEQ ID NO: 22)

wherein A* represents nucleotides functionalized to incorporate a cholic acid functionality linked via a 2'-O-pentyl-amino linking group to the 2' position of the designated nucleotide. HPLC retention times are shown in Table 1 below.

Please amend the paragraph on page 32, line 34 through page 33, line 13 as shown below:

An aliquot of the oligonucleotide-maleimide conjugate of Example 9-A-1 (about 50 O.D. units, 300 nmols) is lyophilized in a microfuge tube. SV40 peptide (pro-asp-lys-lys-arg-lys-cys) (SEQ ID NO: 24) (2.5 mg, about 2.5 µmols) is taken up in phosphate buffer (800 µl, 0.1 M, pH 7.0) and added to the oligonucleotide-maleimide conjugate containing tube. The contents of the tube are stirred overnight under an argon atmosphere. The reaction mixture is passed through a Sephadex G-25 column and the oligonucleotide-peptide conjugate fractions are identified by HPLC. Isolation of the product from product-bearing fractions via HPLC and desalting on Sephadex G-25 will yield an oligonucleotide of the sequence:

Oligomer 27: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 25)

wherein A* represents a nucleotide functionalized to incorporate a SV40 peptide functionality linked via a 2'-O-pentyl-amino-sulfo-SMCC (sulfosuccinimidyl-4-(N-

maleimidomethyl)cyclohexane-1-carboxylate) linking group to the 2' position of the designated nucleotide.

Please amend the paragraph on page 33, line 30 through page 34, line 21 as shown below:

A solution of calf intestinal alkaline phosphatase (Boehringer Mannheim) (20.6 mg, 2.06 ml, 147 nmol) is spun at 4°C in a Centricon microconcentrator at 6000 rpm until the volume is less than 50 µl. It is then redissolved in 1 ml of cold Tris buffer (pH 8.5, 0.1M containing 0.1 NaCl and 0.05 M $MgCl_2$) and concentrated twice more. Finally the concentrate is dissolved in 400 µl of the same buffer. This solution is added to the activated oligonucleotide from Example 9-B-1 and the solution stored for 18 hrs at room temp. The product is diluted to approximately 30 ml and applied to a Sephadex G-25 column (1 x 20 cm, chloride form) maintained at 4°C. The column is eluted with 50 nM Tris-Cl pH 8.5 until the UV absorbance of the fractions eluted reach near zero values. The column is then eluted with a NaCl salt gradient 0.05 M to 0.75 M (150 ml each). The different peaks are assayed for both oligonucleotide and alkaline phosphatase activity and the product bearing fractions are combined. Typically the first peak will be excess enzyme, the second peak the oligonucleotide-protein conjugate and the third peak unreacted oligonucleotide. Isolation of the product from the product-bearing fractions via HPLC and desalting on Sephadex G-25 will yield an oligonucleotide of the sequence:

Oligomer 28: CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 26)

wherein A* represents a nucleotide functionalized to incorporate an alkaline phosphatase functionality linked via an 2'-O-pentyl-amino-sulfo-SMCC (sulfosuccinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate) linking group to the 2' position of the designated nucleotide.

Please amend the paragraph on page 34, lines 24-33 as shown below:

Utilizing the method of Example 9-A-1 the intermediate amino linker oligonucleotide of Example 2-A is reacted with sulfo-SMCC reagent. The isolated oligonucleotide-

maleimide conjugate is then further reacted with SV40 peptide as per Example 9-A-2. This will give an oligonucleotide of the structure:

Oligomer 29: TTG CTT* CCA TCT TCC TCG TC (SEQ ID NO: 27)

wherein T* represents a nucleotide functionalized to include a peptide linked via an extended linker to the heterocyclic base of a 2'-deoxyuridine nucleotide.

Please amend the paragraph on page 35, lines 3-14 as shown below:

Utilizing the method of Example 9-B-1 the 2'-O-methyl derivatized intermediate amino linker oligonucleotide of Example 6-A is reacted with DSS reagent. The isolated oligonucleotide-disuccinimidyl suberate conjugate is then further reacted with a lysine containing Nuclease RNase H using the method of Example 9-B-2. This will give an oligonucleotide of the structure:

Oligomer 30: $C_sC_sC_s$ $A_sG_sG_s$ $C_sU_sC_s$ A_sG_sA-3'-protein (SEQ ID NO: 28)

wherein protein represents RNase H, the subscript "s" represents a phosphorothioate inter-nucleotide backbone linkage and each of the nucleotides of the oligonucleotide includes a 2'-O-methyl group thereon.

Please amend the paragraph on page 35, lines 18-29 as shown below:

Utilizing the method of Example 9-B-1 the 2'-O-methyl derivatized intermediate amino linker oligonucleotide of Example 6-A (Oligomer 6) is reacted with DSS reagent. The isolated oligonucleotide-disuccinimidyl suberate conjugate is then further reacted with a lysine containing Staphylococcal Nuclease using the method of Example 9-B-2. This will give an oligonucleotide of the structure:

Oligomer 31: 5'-protein-$C_sC_sC_s$ $A_sG_sG_s$ $C_sU_sC_s$ A_sG_sA 3' (SEQ ID NO: 29)

wherein protein represents Staphylococcal Nuclease, the subscript "s" represents a phosphorothioate inter-nucleotide backbone linkage and each of the nucleotides of the oligonucleotide includes a 2'-O-methyl group thereon.

Please amend the paragraph on page 37, line 24 through page 38, line 20 as shown below:

A series of oligonucleotides were synthesized utilizing standard synthetic procedures (for un-functionalized oligonucleotides) or the procedure of Example 3-A above for oligonucleotides having a 5'-terminus amino linker bearing oligonucleotide or the procedure of Example 3-B for 5'-terminus cholic acid-bearing oligonucleotides. Each of the oligonucleotides had the following 5-LO antisense sequence: 5' TCC AGG TGT CCG CAT C 3' (SEQ ID NO: 30). The nucleotides were synthesized on a 1.0 μmol scale. Oligomer 32 was the parent compound having normal phosphodiester inter-nucleotide linkages. Oligomer 33 incorporated phosphorothioate inter-nucleotide linkages in the basic oligonucleotide sequence. Oligomer 34 is a an intermediate oligonucleotide having a 5'-aminolink at the 5'-terminus of the basic oligonucleotide sequence and Oligomer 35 was a similar 5'-aminolink compound incorporating phosphorothioate inter-nucleotide linkages. Oligomer 36 is a 5'-terminus cholic acid conjugate of the basic phosphodiester oligonucleotide sequence while Oligomer 37 is a similar 5'-cholic acid conjugate incorporating phosphorothioate inter-nucleotide linkages. Oligomers 32 and 33 were synthesized in a "Trityl-On" mode and were purified by HPLC. Oligomers 34 and 35 were synthesized as per Example 30-A above without or with Beaucage reagent treatment, to yield phosphodiester or phosphorothioate inter-nucleotide linkages, respectively. Oligomers 36 and 37 were prepared from samples of Oligomers 34 and 35, respectively, utilizing a solution of cholic acid N-hydroxysuccinimide ester (Compound 1) 1 dissolved in DMF as per Example 3-B. Oligomers 36 and 37 were purified by HPLC. The products were concentrated and desalted in a Sephadex G-25 column. Gel electrophoresis analyses also confirmed a pure product with the pure conjugate moving slower than the parent oligonucleotide or 5'-amino functionalized oligonucleotide.

Please amend the paragraph on page 39, line 36 through page 40, line 10 as shown below:

An oligonucleotide of the sequence:

Oligomer 38: GGA* CCG GA*A* GGT A*CG A*G (SEQ ID NO: 31)

wherein A* represents a nucleotide functionalized to incorporate a pentylamino functionality at its 2'-position was synthesized in a one micromole scale utilizing the method of Example 7-B. The oligonucleotide was purified by reverse phase HPLC, detritylated and desalted on

Sephadex G-25. PAGE gel analysis showed a single band. A further oligonucleotide, Oligomer 39, having the same sequence but without any 2'-O-amino linker was synthesis in a standard manner. A complementary DNA oligonucleotide of the sequence:

Oligomer 40: CCT GGC CTT CCA TGC TC. (SEQ ID NO: 32)

was also synthesized in a standard manner as was a complementary RNA oligonucleotide of the sequence:

Oligomer 41: CCU GGC CUU CCA UGC UC (SEQ ID NO: 33)

Please amend the paragraph on page 41, line 11 through page 42, line 1 as shown below:

For this test, a phosphorothioate oligonucleotide analog of the sequence:

Oligomer 42: CTG TCT CCA TCC TCT TCA CT (SEQ ID NO: 34)

was used as the basic sequence. This sequence is designed to be complementary to the translation initiation region of the E2 gene of bovine papilloma virus type 1 (BPV-1). Oligomer 42 served as the positive control and standard for the assay. Oligomer 3 (from Example 4 above) served as a second test compound. It has the same basic sequence except it is a phosphorothioate oligonucleotide and further it has a cholic acid moiety conjugated at the 3'-end of the oligonucleotide. Oligomer 2 (from Example 2 above) served as a third test compound. Again it is of the same sequence, it is a phosphorothioate oligonucleotide and it has a cholic acid moiety conjugated at the 5'-end. Oligomer 5 (from Example 5 above) served as a fourth test compound. Once again it has the same sequence, is a phosphorothioate oligonucleotide and it has a cholic acid moiety conjugated at both the 3'-end and 5'-end. A fifth test compound was a phosphorothioate oligonucleotide with no significant sequence homology with BPV-1. A sixth test compound was a further phosphorothioate oligonucleotide with no significant sequence homology with BPV-1. The last test compound, the seventh test compound, was a phosphorothioate oligonucleotide with cholic acid conjugated to the 3'-end but having no significant sequence homology with BPV-1. Compounds five, six and seven served as negative controls for the assay.

Please amend the paragraph on page 43, line 1 through page 44, line 1 as shown below:

For this test the absence of an oligonucleotide in a test well served as the control. All oligonucleotides were tested as 2'-O-methyl analogs. For this test an oligonucleotide of the sequence:

Oligomer 43: CCC AGG CUC AGA (SEQ ID NO: 35)

where each of the nucleotides of the oligonucleotide includes a 2'-O-methyl substituent group served as the basic test compound. The second test compound of the sequence:

Oligomer 44: 5'-CHA CCC AGG CUC AGA (SEQ ID NO: 6)

wherein CHA represents cholic acid and where each of the nucleotides of the oligonucleotide includes a 2'-O-methyl substituent group, was also of the same sequence as the first test compound. This second test compound included cholic acid conjugated to its 5'-end and was prepared as per the method of Example 3 utilizing 2'-O-methyl phosphoramidite intermediates as identified in Example 7-C. The third test compound of the sequence:

Oligomer 45: CCC AGG CUC AGA 3'-CHA (SEQ ID NO: 7)

wherein CHA represents cholic acid and where each of the nucleotides of the oligonucleotide includes a 2'-O-methyl substituent group was also of the same sequence as the first test compound. The third test compound included cholic acid conjugated to its 3'-end and was prepared as per the method of Example 4 utilizing 2'-O-methyl phosphoramidite intermediates as identified in Example 7-C. The fourth test compound was a 2'-O-Me oligonucleotide of a second sequence:

Oligomer 46: GAG CUC CCA GGC (SEQ ID NO: 36)

where each of the nucleotides of the oligonucleotide includes a 2'-O-methyl substituent group. The fifth test compound was of sequence:

Oligomer 47: 5'-CHA GAG CUC CCA GGC. (SEQ ID NO: 8)

wherein CHA represents cholic acid and where each of the nucleotides of the oligonucleotide includes a 2'-O-methyl substituent group. It was of the same sequence as the fifth test compound. This test compound included cholic acid conjugated to its 5'-end and was prepared as per the method of Example 3 utilizing 2'-O-methyl phosphoramidite intermediates as identified in Example 7-C.

Please amend the paragraph on page 44, lines 2-4 as shown below:

A sixth test compound was a randomized oligonucleotide of the sequence:

Oligomer 48: CAU GCU GCA GCC (SEQ ID NO: 37).

Please amend the paragraph on page 46, lines 13-25 as shown below:

Multiple batches of an oligonucleotide of the sequence:

Oligomer 49:

$T_sG_sG_s$ $G_sA_sG_s$ $C_sC_sG_s$ $T_sA_sG_s$ $C_sG_sA_s$ $G_sG_sC_s$-3'AL (SEQ ID NO: 38)

wherein AL represents a 3'-aminolinker and "s" represents a phosphorothioate inter-nucleotide backbone linkage were synthesized as per the procedure of Example 4 on 10 μmol scales in the standard manner on the DNA synthesizer utilizing phosphoramidite methodology employing 3'-amine-ON solid support available from Clontech. During the synthesis, the phosphorothioate backbone was formed by the Beaucage reagent. The oligonucleotide was deprotected and purified using standard protocols.

Please amend the paragraph on page 50, lines 5-16 as shown below:

The following oligonucleotides having phosphodiester inter-nucleotide linkages and a 2'-aminolinker at the 3' terminal nucleotide were synthesized:

Oligomer 50: GGC GUC UCC AGG GGA UCU GAC* (SEQ ID NO: 39)

Oligomer 51: TCT GAG TAG CAG AGG AGC TC* (SEQ ID NO: 40)

wherein C* represents a nucleotide functionalized to incorporate a propyl-N-phthalimido functionality. Oligomer 50 is antisense to the Cap region of CMV and Oligomer 51 is antisense to an ICAM sequence. The oligonucleotides were synthesized on a 3 μmol scale. Upon completion of synthesis they were deprotected using standard protocols and purified by reverse phase HPLC, detritylated and desalted.

Please amend the paragraph on page 51, lines 5-12 as shown below:

To the solution resulting from Example 20-A was added 2 mg of 5-(iodoacetamide)-*o*-phenanthroline reagent followed by shaking overnight. The conjugate was purified by a size exclusion column and reverse phase HPLC to yield

Oligomer 52: GGC GUC UCC AGG GGA UCU GAC-2'PHA (SEQ ID NO: 41)

wherein PHA represents a nucleotide functionalized at its 2'- position with phenanthroline via a thiol linker of the structure 2'-O-$(CH_2)_3$-NH-C(=O)-CH_2-S-CH_2-C(=O)-NH-.

Please amend the paragraph on page 51, lines 14-21 as shown below:

To the solution resulting from Example 20-A was added 2 mg of 5-(iodoacetamide)-O-phenanthroline reagent followed by shaking overnight. The conjugate was purified by a size exclusion column and reverse phase HPLC to yield

Oligomer 53: TCT GAG TAG CAG AGG AGC TC-2'PHA (SEQ ID NO: 42)

wherein PHA represents a nucleotide functionalized at its 2'- position with phenanthroline via a thiol linker of the structure 2'-O-$(CH_2)_3$-NH-C(=O)-CH_2-S-CH_2-C(=O)-NH-.

Please amend the paragraph on page 51, line 28 through page 52, line 4 a shown below:

The following oligonucleotide having phosphodiester inter-nucleotide linkages and a 2'-aminolinker at an internal position is synthesized utilizing the uridine 2'-aminolinker of Example 18:

Oligomer 54: GGC CAG AUC UGA GCC UGG GAG CU*C UGU GGC C (SEQ ID NO: 43)

wherein U* represents a nucleotide functionalized to incorporate a propyl-N-phthalimido functionality. Oligomer 50 is an oligonucleotide corresponding to positions G_{16} to C_{46} of TAR RNA.

Please amend the paragraph on page 55, line 32 through page 56, line 12 as shown below:

Oligomer 14 (*i.e.*, TTG CTT CCA* TCT TCC TCG TC (SEQ ID NO: 44) wherein A* represents 2'-O-pentyl amino adenosine, Example 7-C, 100 O.D. units, 595 nmols, based on the calculated extinction coefficient of 1.6792 x 10^6 OD units) was dried and dissolved in 500 ml of 0.2M $NaHCO_3$ buffer pH 8.1 and treated with 25 mg of N-hydroxysuccinimidyl-4-azidobenzoate (HSAB, 96 μmols, available both from Pierce & Sigma)) dissolved in 500 μl of DMF. The reaction was allowed to react overnight at 37°C and passed twice over Sephadex G-25 column (1 x 40 cm). The oligonucleotide fraction was purified by reverse-phase HPLC. The product had the HPLC retention time of 38.79 min while the parent oligonucleotide had the retention time of 33.69 min. (5% → 40% CH3CN in 60 min.) in reverse phase column.

Please amend the paragraph on page 56, line 30 through page 57, line 14 as shown below:

Utilizing the protocol described in Procedure B-1-b, the melting temperatures of various of the 2-aminolinked conjugate oligomers of the invention against a complementary DNA strand were obtained. The conjugate oligomers were compared to an oligomer of the same sequence bearing a 2'-O-pentylamino group. An un-modified, *i.e.*, wild type, strand of the same sequence was also tested for comparison purposes. Both single site and multiple site conjugated oligomers were tested. As is shown in Table 5, the T_m and the ΔT_m/modification, both as compared to 2'-pentylamino bearing oligomer, were measured. The wild type sequence is:

Oligomer 55:

CTG TCT CCA TCC TCT TCA CT (SEQ ID NO: 45)

the single site sequence is:

Oligomer 12:

CTG TCT CCA* TCC TCT TCA CT (SEQ ID NO: 10)

and the multiple site sequence is:

Oligomer 13:

CTG TCT CCA* TCC TCT TCA* CT (SEQ ID NO: 11)

where A* represents a site of conjugation.

Please amend the paragraph on page 59, lines 23-29 as shown below:

Oligomer 55:

$T_sG_sG_s$ $G_sA_sG_s$ $C_sC_sG_s$ $T_sA^*{}_sG_s$ $C_sG_sA_s$ $G_sG_sC_s$ (SEQ ID NO: 46)

wherein A^* represents an adenosine nucleotide funtionalized to incorporate a 2'-O-pentylamino linking group is synthesized as per Example 7. This oligonucleotide is then converted into a thiol linker compound as per the procedure described for Oligomer 50 in Example 20.

Please amend the paragraph on page 61, line 9 to page 62, line 4 as shown below:

The effect of conjugation of an oligonucleotide with folic acid was determined by the inhibition of ICAM-1 utilizing the method of Chiang, *et al.*, *J. Biol. Chem.* **1991**, *266*, 18162. Utilizing this method, human lung epithelial carcinoma cells (A549 cells) were grown to confluence in 96 well plates. Medium was removed and the cells were washed with folic acid free medium three times. Folic acid free medium was added to the cells and increasing concentrations of an ICAM-1 specific antisense phosphorothioate oligonucleotide having the sequence 5'-TGG GAG CCA TAG CGA GGC-3' (SEQ ID NO: 47), either free or conjugated to folic acid, was added to the incubation medium. This oligonucleotide is an 18 base phosphorothioate oligonucleotide that targets the AUG translation initiation codon of the human ICAM-1 mRNA (Chiang *et al.*, *J. Biol. Chem.* **1991**, *266*, 18162). The oligonucleotides were incubated with the A549 cells for 24 hours then ICAM-1 was induced by adding 2.5 ng/ml tumor necrosis factor-α to the medium. Cells were incubated an additional 15 hours in the presence of tumor necrosis factor-α and oligonucleotide. ICAM-1 expression was determined by a specific ELISA as described by Chiang, *et al.*. We had previously demonstrated that the addition of the test oligonucleotide to incubation medium alone does not result in inhibition of ICAM-1 expression. However formulation of the test oligonucleotide with cationic liposomes results in at least a 1000 fold increase in potency and also correlates with the appearance of the oligonucleotide in the nucleus (Bennett, *et al.*, *Molecular Pharmacology* **1991**, *41*, 1023). The results of this test are shown in Table 6. At

the 30uM level, the folic acid conjugated oligonucleotide shows an approximate 40% enhancement in activity.